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(54) **Title:** MEDICAL TREATMENT USING THYROID HORMONES

(57) **Abstract**

Central nervous system ischemia is prevented or minimised in a patient who has suffered an acute insult by administering a protective amount of a thyroid hormone such as levothyroxine, liothyronine, L-3,3',5'-triiodothyronine or L-3,5-diiodothyronine, preferably in the form of their sodium salts. An initial bolus dose of the thyroid hormone may be given before initiation of the continuous administration. The treatment is particularly applicable to the treatment of cerebral ischemia following cardiac arrest.

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MEDICAL TREATMENT USING THYROID HORMONES

This invention relates to the treatment of central nervous system ischemia. Examples of central nervous system ischemia include cerebral ischemia and spinal column ischemia. The central nervous system ischemia may result from an acute insult such as cardiac arrest.

The present invention provides a method of minimising central nervous system ischemia in a patient who has suffered cardiac arrest, in which method a protective amount of at least one thyroid hormone is administered to the patient. The thyroid hormone may be administered as a continuous infusion or as an initial bolus dose followed by continuous infusion.

The thyroid hormone may be L-3,5,3',5'-tetraiodothyronine (levothyroxine or LT4) preferably in the form of its sodium salt (levothyroxine sodium), L-3,5,3'-triiodothyronine (liothyronine or LT3) preferably in the form of its sodium salt (liothyronine sodium), L-3,3',5'-triiodothyronine (LrT3) preferably in the form of its sodium salt, L-3,5-diiodothyronine (LT2) preferably in the form of its sodium salt or mixtures thereof.

When the thyroid hormone is levothyroxine or a salt thereof, the amount of levothyroxine given as an initial bolus dose may lie in the range 500 to 5000 µg. The amount of levothyroxine administered by continuous infusion to the patient preferably lies in the range about 0.1 to about 15, preferably about 0.5 to about 10, more preferably about 1 to about 4 µg/kg/hr.

When the thyroid hormone is liothyronine or a salt thereof, the amount of liothyronine given as a single dose may lie in the range 30 to 2500 μg. The amount of liothyronine administered by continuous infusion to the patient preferably lies in the range about 0.01 to about 7.5, preferably about 0.03 to about 5, more preferably about 0.06 to about 1 μg/kg/hr.

When the thyroid hormone is LrT3 or a salt thereof, the amount of LrT3 given as a single dose may lie in the range 1000 to 10000 μg. The amount of LrT3 administered by continuous infusion to the patient preferably lies in the range about 0.2 to about 30, preferably about 1 to about 20, more preferably about 2 to about 8 μg/kg/hr.

The amount of thyroid hormone in the continuous infusion fluid is preferably such that the required dose is administered by the infusion of 0.1 to 10 ml/kg/hr of the infusion fluid.

The thyroid hormone is preferably administered by intravenous injection of a sterile solution of the thyroid hormone in a pharmaceutically acceptable solvent, for example saline solution. The solution may also contain other pharmaceutically acceptable components such as potassium and calcium chloride (Ringers solution USP) or pH-controlling agents.

A further aspect of the present invention provides use of a thyroid hormone in minimising central nervous system ischemia in a patient who has suffered cardiac arrest. Another aspect of the present invention provides use of a thyroid hormone in the manufacture of a medicament for minimising central nervous system ischemia in a patient who has suffered cardiac arrest.

Yet another aspect of the present invention provides a pharmaceutical composition for minimising central nervous system ischemia in a patient who has suffered cardiac arrest comprising a protective amount of a thyroid hormone as the main ingredient in conjuction with a pharmaceutically acceptable diluent or carrier.

For example, in a patient suffering from cardiac arrest the heart ceases to circulate blood around the body. The cessation of the pumping action of the heart stops the supply of blood to vital organs, such as the brain, and severe damage can be caused to those vital organs. It is therefore essential that any patient who suffers a cardiac arrest is resuscitated as soon as possible after the arrest so as to minimise the potential damage to vital organs. The medical profession is constantly seeking treatments which reduce the chances of this damage to vital organs occurring after cardiac arrest. One preferred aspect of the present invention relates to a treatment to be administered to patients who have suffered a cardiac arrest to prevent or minimise cerebral ischemia. There are already many well established treatments which are given to patients following cardiac arrest, for example dopamine, dobutamine, lidocaine, isoproterenol, furosemide, heparin, mannitol, antibiotics (such as cefluroxime and imipenim / citastin) or vaopressin. It is intended that the treatment which forms the subject of the present invention should be additional to these established treatments.

The administration of the thyroid hormone should commence as soon as possible after the cardiac arrest. In a hospital situation where medical attention can be obtained very rapidly, the patient can be resuscitated

and the administration of the thyroid hormone can be initiated within minutes. However, when the patient suffers cardiac arrest away from a hospital a much longer period of time will elapse before the patient can be resuscitated and the administration of the thyroid hormone can commence. It is however important that administration commences as soon as possible. Administration should be initiated as soon as the patient is receiving medical attention. If the patient is initially attended by a paramedic or ambulanceman then that person should initiate the administration before the patient is seen by a qualified medical practitioner. In a preferred method of treatment the patient who has suffered the cardiac arrest is initially given a bolus dose of the thyroid hormone. The initial bolus dose may be in the range of about 500 μg to about 5000 μg. Continuous infusion at the rates described above should then be initiated as soon as possible after the administration of the initial bolus dose.

Patients who have suffered a cardiac arrest are subject to careful monitoring by the medical practitioner responsible for their treatment. The administration of thyroid hormone will be stopped only when the medical practitioner believes that it is no longer beneficial to the patient. When the patient is in a stable haemodynamic and neurological situation, the medical practitioner may decide to cease administration of the thyroid hormone either immediately or, preferably, by means of a gradual reduction of the administered dose over a period of time. It is envisaged that after 18 to 24 hours the dose may start to be gradually reduced and that administration may cease after a further 24 to 48 hours if no adverse effects on the patient are observed.

The cerebral-protecting effect of the continuous administration of a thyroid hormone has been demonstrated by the following experiments performed on dogs. In the experiments each dog was anesthetised and surgically fitted with basic instrumentation, subjected to ventricular fibrillation to cause nine minutes of cardiac arrest and then resuscitated. Of the 33 dogs used 14 were not given any thyroid hormone and the remainder were continuously infused with either 7.5 µg/kg/hr or 15 µg/kg/hr of levothyroxine sodium over the experimental period of 24 hours.

Preparation of the experimental animals

Thirty-three fasted adult male mongrel dogs weighing between 14.5 and 24.1 kg were premedicated with 1.5 mg/kg s.c. morphine sulphate (Elkins-Sinn, Inc., Cherry Hill, New Jersey) and anesthetised (Foregger Fluomatic, Smithtown, New York) with 5% halothane (Halocarbon Laboratories, North Augusta, South Carolina) in oxygen via face mask and demand ventilation. The dogs were mechanically ventilated (Air-Shields Ventimeter Ventilator, Hatboro, Pennsylvania) with 1-2% halothane to maintain surgical anaesthesia and suppression of corneal reflexes. Paralysing agents were not used. Expired CO_2 tension was monitored and maintained between 4% and 5% (Beckman LB-2, Fullerton, California). Deep esophageal temperature was monitored and maintained at 39.0 ± 1.0°C before arrest and for at least one hour after resuscitation with a homeothermic blanket system (Model 50-7095, Harvard Apparatus, South Natick, Massachusetts). A urethral catheter was inserted to maintain an empty bladder.

Two venous catheters were inserted; one passed by way of the left external jugular vein to the right

atrium for administration of resuscitation drugs, and the other into a muscular branch of the left femoral vein for fluid administration. Arterial blood pressure was measured through a catheter placed in a muscular branch of the left femoral vein for fluid administration. Arterial blood pressure was measured through a catheter placed in a muscular branch of the left femoral artery (Statham P23XL transducer, Gould, Inc., Oxnard, California). Subcutaneous disk electrodes (Grass Instrument Co. E5SH Silver Cup Electrodes, Quincy, Massachusetts) were placed to monitor lead II electrocardiogram (ECG). Each animal received intravenously 500 ml of 0.45% sodium chloride (Abbott Laboratories, North Chicago, Illinois) with 1.5 meq/kg of sodium bicarbonate (Fisher Scientific, Fair Lawn, New Jersey) to assure adequate hydration before arrest, followed by a continuous intravenous drip of 0.45% sodium chloride at 2 ml/kg/hr (IVAC 530, San Diego, California) throughout the recovery period. A thoracotomy and pericardiectomy at the left fifth interspace facilitated direct cardiac compression. The correct placement of the jugular vein catheter was confirmed by direct palpation of the vena cava. All catheters and electrical leads were passed subcutaneously to exit the skin in the dorsal midscapular region for later attachment to a dog jacket and hydraulic/electric swivel. Pulsatile and mean arterial blood pressure (MAP), ECG, and end-expiratory CO_2 were continuously recorded on a six-channel oscillograph (Model 200, Gould-Brush, Cleveland, Ohio).

Cardiac Arrest

At the conclusion of surgical instrumentation, halothane was discontinued while ventilation was continued with room air (Model 607, Harvard Apparatus,

South Natick, Massachusetts) in order to reduce and standardize the level of anaesthesia at which ventricular fibrillation was induced. As soon as corneal reflexes returned (stage 3, plane 1 of surgical anaesthesia), the heart was fibrillated by delivering a 10-15 second, 60 Hz, 2 msec square-wave stimulus to the left ventricular epicardium. Ventilation was discontinued while circulatory arrest was confirmed by ECG, MAP, and direct observation of the heart.

Resuscitation

After 9 minutes of normothermic ventricular fibrillation, ventilation was restarted while direct cardiac massage maintained MAP above 75 mmHg. Vasopressor support was initiated by central venous administration of 40 µg/kg epinephrine (Berlex Laboratories, Inc., Wayne, New Jersey) and 10 µg/kg/min dopamine (Abbott Laboratories), followed in rapid succession by 1 mg/kg lidocaine (Elkins-Sinn, Inc.), 4 meq/kg sodium bicarbonate, and 25 mg/kg calcium chloride (American Regent Laboratories, Inc., Shirley, New York). Cardioversion was attempted by delivering a 20-50 J charge (Lifepak 6 defibrillator/monitor, Physio Control, Redmond, Washington) with 31 cm^2 paddles placed on the right and left ventricular surfaces. Additional drugs or charges were administered as indicated by MAP and ECG monitoring.

Post-resuscitation dopamine infusion maintained MAP above 75 mmHg as long as necessary but for not longer than 6 hours (typically only 30 min). A rubber catheter was passed through the chest wall and sealed in place with a purse string suture; intermittent suction (Gomco Thoracic Pump, Gomco Corp., Buffalo, New York) was used to evacuate any air or fluid accumulation after chest

closure. Mechanical ventilation continued until spontaneous ventilation ensued, but for not longer than 6 hours (typically only 30 min). Extubation occurred upon return of the gag reflex.

Four dogs were not placed on the room air ventilator subsequent to completion of the surgical preparation, but were instead maintained on 0.5% halothane. The heart was fibrillated. Upon confirmation of ventricular fibrillation, cardioversion was attempted immediately; resuscitation drugs were administered only as indicated. This group is identified below as the control group. Halothane/oxygen was replaced with room air ventilation after chest closure. In this way, these animals received the full extent of the surgical insult while sustaining the shortest possible period of ventricular fibrillation and resuscitation. The three other experimental groups were subjected to a controlled 9 min cardiac arrest, in contrast to the control, which had minimum ischemia (approx. 30 sec) but otherwise identical surgical manipulations.

All dogs were given 10 mg/kg i.m. Spectinomycin (Ceva Laboratories, Inc., Overland Park, Kansas). No animals in this study exhibited behaviours that required post-operative analgesia. Each dog was placed in a jacket and swivel (Alice King Chatham Medical Arts, Los Angeles, California) permitting 3 electrical and 3 hydraulic connections while allowing free movement about the cage. Dogs surviving to 24 hours post-arrest were killed with 120 mg/kg i.v. sodium pentobarbital following final neurologic deficit scoring and blood sampling. Post-mortem examinations of the heart, lungs, and wound sites were conducted to identify iatrogeny and heart worm infestations. Animals were excluded from

this study if their cause of death could be attributed to any cause (haemorrhage, pneumothorax, catheter placement, etc.) other than neurologic impairment.

Blood Sampling

Ten arterial blood samples were taken for thyroid hormones, pH, hematocrit and plasma glucose measurement. The first sample was drawn immediately after the insertion of femoral artery catheter and served as the baseline. Ventilation and bicarbonate administration were then manipulated as needed during surgery to maintain arterial blood pH between 7.38 and 7.41 (pH/Blood Gas Analyser 113, Instrumentation Laboratories, Lexington, Massachusetts). Plasma glucose concentrations were determined by the glucose oxidase method using an automated glucose analyzer (YSI Model 23A, Yellow Springs, Ohio). Hematocrit measurements were made using standard microcentrifuge tubes. The second sample was taken immediately before the induction of ventricular fibrillation (pre-arrest), and the third sample was taken immediately after the animal was resuscitated (post-arrest). The remaining samples were taken 0.5,1, 2, 4, 6, 12 and 24 hours post-arrest. At each sample time, the MAP, heart rate (HR), and body temperature (mid-esophageal while on the operating table; rectal when placed in a recovery cage) were noted. Total urine output was also noted until the bladder catheter was removed (not later than 6 hours post-arrest).

Thyroid Hormone Assay

At all ten sample times, arterial blood samples for the thyroid assays (total thyroxine, T4; free thyroxine, FT4; total 3,5,3'-triiodothyronine, T3; free

3,5,3'-triiodothyronine, FT3; and reverse 3,3',5'-triiodothyronine, rT3) were withdrawn into clot activated sample tubes (Vacutainer SST 6510, Becton Dickinson, Rutherford, New Jersey) and allowed to clot at room temperature for 30 minutes before they were centrifuged at 1300 g for 10 minutes. The serum was removed and stored at -20°C. The thyroid hormones were assayed using standard radioimmunoassay methods.

Neurologic Deficit Assessment

A well-standardised score was assigned 1, 2, 6, 12 and 24 hours post-arrest to assess neurologic deficit. Interobserver variability was resolved through consultation of the detailed description of each neurologic functional level. Of the 100 points possible, 18 are assigned to consciousness, 18 to respiratory function, 16 to cranial nerve function, 20 to spinal nerve function, and 28 to motor function as set out in Table 1.

Table 1

	Score
CONSCIOUSNESS (Range 0-18)	
Normal, consistently alert	0
Continually conscious but clouded	3
Intermittently conscious, aroused with minimum effort	6
Stuporous, aroused with persistent effort	12
Light coma, reflex movement only	15
Deep coma, no movement	18
RESPIRATION (Range 0-18)	
Normal, extubated and normal	0
Extubated/abnormal, extubated but normal	6
Intubated/spontaneous, intubated but off ventilator	12
On ventilator, intubated and on ventilator	18
CRANIAL NERVES (Range 0-16)	
Corneal reflex	
Strong, consistently blinks in response or saline in eye area	0
Weak, inconsistently blinks in response to touch or saline in eye area	1
Absent, does not respond to touch or saline in eye area	2
Pupillary light reflex	
Strong, constricts pupil to light quickly and completely	0
Weak, constricts pupil to light slowly and/or incompletely	1
Absent, does not constrict pupil to light or pupil fixed and constricted	2

Facial sensation

Strong, reacts consistently to touch in any area of face	0
Weak, reacts to touch only in certain areas or inconsistently	1
Absent, does not react to touch in any facial area	2

Gag reflex

Strong, rapid and strong reaction to endotracheal tube or forceps in throat	0
Weak, slow, weak, or inconsistent reaction	1
Absent, no gag response on stimulation of throat	2

Jaw reflex

Strong,strongly resists rapid opening of jaw	0
Weak, weakly resists rapid opening of jaw	1
Absent, jaw flaccid	2

Pinna reflex

Strong, twitches ear in response to touch on outer/inner hairs	0
Weak, twitches ear in response to touch on deep inner hairs only	1
Absent, does not move ear in response to touch	2

Olfactory reflex

Strong, strong reaction to acetic acid near nostril	0
Weak, weak reaction to acetic acid near nostril	1
Absent, no reaction	2

Swallowing reflex

Strong, consistently swallows water when injected into mouth	0
Weak, inconsistent swallowing of water	1

Absent, does not swallow	2

SPINAL NERVES (Range 0-20)

Limb tone (fore/hind)

Normal, limb has tone without stiffness	0/0
Spastic, stiff tone; resists movement	2/2
Flaccid, no tone	4/4

Pain reflex (fore/hind)

Strong, quick, complete withdrawal from toe pinch	0/0
Weak, slow, incomplete, or inconsistent withdrawal from toe pinch	2/2
Absent, no withdrawal from toe pinch	4/4

Knee jerk

Strong, normal slow response	0
Weak, incomplete response	2
Absent, no response or hyper-reflexive	4

MOTOR FUNCTION (Range 0-28)

Normal, walks normally	0
Minimal ataxia, walks with some impairment of gait	2
Ataxia, just able to walk	4
Stands spontaneously, falls with a few steps	6
Stands if posed, falls with any movement	8
Sits spontaneously, without falling	10
Sits if posed, falls with any movement	12
Spontaneous dorsal recumbancy	14
Posed dorsal recumbancy	16
Spontaneous purposeful movement, unprovoked, nonconvulsive movement	18
Provoked purposeful movement, provoked non-convulsive movement	20

Reflex, spastic, or convulsive movement only	24
No movement	28

Protocols and Experimental Groups

The animals in this study were divided into four separate groups as outlined below. There are no differences among the groups in terms of the general preparation or instrumentation before the induction of cardiac arrest.

Controls

Four dogs received not more than 30 seconds of ventricular fibrillation (as described above) before resuscitative efforts were begun. These animals received no therapy or medications other than those described in the basic preparation.

Untreated

The 10 dogs in the untreated group received 9 minutes of normothermic ventricular fibrillation before resuscitative efforts were begun. These animals received no therapy or medications other than those described in the basic preparation.

Treated-7.5

The 11 dogs in the treated-7.5 group received 9 minutes of normothermic ventricular fibrillation, exactly as in the untreated group. Immediately following initial cardiopulmonary resuscitation, however, the treated-7.5 group received a constant infusion of 7.5 μg/kg/hr levothyroxine sodium (L-T4;

Boots Pharmaceuticals, Inc., Lincolnshire,Illinois) for the duration of the recovery period (24 hours) via the central venous catheter. No other therapy or medications were administered to the treated dogs in this group other than those described above in respect of their preparation and resuscitation.

Treated-15

The 8 dogs in the treated-15 group were identical to the treated-7.5 group with the exception that they received 15 μg/kg/hr L-T4 post-arrest. No other therapy or medications were administered to the treated dogs in this group other than those described above in respect of their preparation and resuscitation.

Statistical Calculations

Comparisons of all physiologic variables were assessed with one way analysis of variance (ANOVA-Scheffe). Neurologic deficit scores were compared non-parametrically using the Mann-Whitney U analysis. An unpaired, 2-tailed Student's t-test was used to assess differences in thyroid hormones between groups at the 12 hour time point (chosen because it was the last sample time at which all dogs were alive and at which the data were the most consistent). Differences in thyroid hormone within groups were assessed between the pre-arrest and 12 hour samples with a paired, 2-tailed Student's t-test. Ten individual hormone samples out of a total of 1650 were greater than 2 standard deviations from the mean of their respective groups and are not included in the analysis. All average data are expressed as mean ± 1 standard error of the mean (SEM). All statistical calculations were performed on a

Macintosh II computer using the Statview SE+Graphics™ software package.

All animals in all groups survived to at least 12 hours post-arrest. Average hours of survival were 24.0 ± 0.0 (controls), 22.0 ± 1.0 (untreated), 21.4 ± 1.2 (treated-7.5), and 21.2 ± 1.6 (treated-15), and were not found to be statistically different by the Fishers' exact test.

Thyroid Hormones

A statistically significant, rapid and sustained decrease in total T4, free T4, total T3, and free T3 was detected by paired Student's t-analyses in both the control and untreated groups following resuscitation. Both the untreated ($p < 0.001$) and control ($p < 0.072$) groups simultaneously showed an acute elevation in reverse T3.

Total and free T4 in the treated-7.5 and treated-15 groups showed significant and sustained elevations following resuscitation. Total and free T3 values, however, differed markedly among the groups. Despite thyroid hormone supplementation, the treated-7.5 group still exhibited significant decreases in both total and free T3. The T3 values in the treated-15 group varied as indicated by larger standard errors; at 12 hours post-arrest both the total and free T3 concentrations in the treated-15 group are significantly elevated above pre-arrest levels (as well as being significantly higher than any of the other groups at 12 hours. Only in the treated-15 group was the plasma concentration of total and free T3 within or above the normal ranges for these hormones during the 24 hours following cardiac resuscitation. Thyroid hormone supplementation

increased reverse T3 levels in both the treated-7.5 and treated-15 groups not only above intra-group pre-arrest levels, but above non-treated groups as well (p=0.0001).

Neurologic Deficit

The neurological deficit scores obtained by each dog is set out below:

Controls

Dog No.	1 hour	2 hour	6 hour	12 hour	24 hour
592	7	3	0	0	3
599	3	3	0	2	0
582	25	19	0	0	0
573	21	14	7	0	0

Untreated

Dog No.	1 hour	2 hour	6 hour	12 hour	24 hour
598	66	61	25	34	dead
600	66	69	45	56	dead
587	61	62	34	31	44
588	64	61	29	41	dead
614	70	70	27	53	dead
619	60	60	29	24	26
604	66	65	27	20	24
608	66	73	45	45	31
574	71	70	54	43	41
572	64	72	36	42	34

Treated 7.5

Dog No.	1 hour	2 hour	6 hour	12 hour	24 hour
603	66	68	24	23	dead
602	70	66	25	22	dead
607	61	68	28	21	25
606	71	67	29	62	48
605	62	60	23	22	dead
594	63	58	24	19	33
593	66	64	26	22	24
591	57	57	26	23	23
595	62	57	25	10	dead
596	66	67	29	31	31

Treated 15

Dog No.	1 hour	2 hour	6 hour	12 hour	24 hour
597	66	68	23	20	19
617	67	64	29	34	27
621	67	64	28	35	dead
618	70	66	34	35	dead
616	63	63	28	22	26
615	66	63	34	35	46
611	66	66	37	19	24
612	65	62	23	21	23
613	72	70	27	19	dead

All dogs survived the first 12 hours post-arrest, but the treated-7.5 group showed the greatest neurologic improvement of the three 9 minute cardiac arrest groups, gaining statistical significance by Mann-Whitney U (non-parametric) at 6 and 12 hours post-arrest compared to

the untreated group. The treated-15 group showed statistically significant improvement compared to the control group at 12 hours post-arrest. The control group, despite heavy doses of morphine, 30 minutes of halothane anaesthesia, a thoracotomy/pericardiectomy, and an acute episode of ventricular fibrillation and cardiopulmonary resuscitation, showed completely restored neurologic function by 12 hours.

At 24 hours, if analysis includes all dogs (dead = 100 neurologic deficit score) there is no statistically significant separation among the 9 min arrest groups. Of the 11 dogs that died before 24 hours post-arrest, all 4 in the treated-7.5 group and 2 out of the 3 in the treated-15 group died suddenly of apparent cardiac pump failure or fibrillation in a manner unlike the more classical neurologic seizures leading to the deaths observed in the control group and in many previous studies using the same basic model. Excluding these "non-neurological deaths" and pooling the two treated groups (to increase sample size) allows for statistical separation from the control group at 24 hours post-arrest. Without pooling, the treated-7.5 group at 24 hours post-arrest ($n = 7$) still shows a statistically significant improvement when compared to the untreated group ($p = 0.031$), but the treated-15 group ($n = 6$) was no longer significantly different when compared to the control group ($p = 0.19$).

Claims

1. A method of minimising central nervous system ischemia in a patient who has suffered cardiac arrest, in which method a protective amount of at least one thyroid hormone is administered to the patient by continuous infusion.

2. A method as claimed in claim 1 wherein the thyroid hormone is levothyroxine, liothyronine, L-3,3',5'-triiodothyronine, L-3,5-diiodothyronine or mixtures thereof.

3. A method as claimed in claim 2 wherein the thyroid hormone is administered in the form of its sodium salt.

4. A method as claimed in claim 3 wherein the thyroid hormone is levothyroxine sodium, liothyronine sodium or mixtures thereof.

5. A method as claimed in claim 1 wherein the thyroid hormone is

a) levothyroxine or its sodium salt and is continuously administered in an amount which lies in the range about 0.1 to about 15 µg/kg/hr, or

b) liothyronine or its sodium salt and is continuously administered in an amount which lies in the range about 0.01 to about 7.5 µg/kg/hr, or

c) LrT3 or a salt thereof and is continuously administered in an amount which lies in the range about 0.2 to about 30 µg/kg/hr.

6. A method as claimed in claim 1 wherein an initial bolus dose of at least one thyroid hormone is administered to the patient before the initiation of the continuous infusion of at least one thyroid hormone.

7. A method as claimed in claim 6 wherein the thyroid hormone comprising the bolus dose is levothyroxine, liothyronine, L-3,3',5'-triiodothyronine, L-3,5-diiodothyronine or mixtures thereof.

8. A method as claimed in claim 6 wherein the thyroid hormone comprising the bolus dose is levothyroxine sodium, liothyronine sodium or mixtures thereof.

9. A method as claimed in claim 6 wherein the thyroid hormone comprising the bolus dose is

a) levothyroxine or its sodium salt and the initial bolus dose lies in the range about 500 μg to about 5000 μg, or

b) liothyronine or its sodium salt and the initial bolus dose lies in the range about 30 μg to about 2500 μg, or

c) LrT3 or its sodium salt and the initial bolus dose lies in the range about 1000 μg to about 10000 μg.

10. A method as claimed in claim 6 wherein the thyroid hormone which is administered by continuous infusion is

a) levothyroxine or its sodium salt and is continuously administered in an amount which lies in the range about 0.1 to about 15 μg/kg/hr, or

b) liothyronine or its sodium salt and is continuously administered in an amount which lies in the range about 0.01 to about 7.5 µg/kg/hr, or

c) LrT3 or its sodium salt and is continuously administered in an amount which lies in the range about 0.2 to about 30 µg/kg/hr.

11. Use of a thyroid hormone in minimising central nervous system ischemia in a patient who has suffered cardiac arrest.

12. Use of a thyroid hormone in the manufacture of a medicament for minimising central nervous system ischemia in a patient who has suffered cardiac arrest.

13. A pharmaceutical composition for minimising central nervous system ischemia in a patient who has suffered cardiac arrest comprising a protective amount of a thyroid hormone as the main ingredient in conjuction with a pharmaceutically acceptable diluent or carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/06772

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 31/195
US CL :514/567

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/567

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS on-line

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	Life Sciences, Volume 50, issued September 1992, (USA), A. Rami et al., "Thyroxine Attenuates Hippocampal Neuronal Damage caused by Ischemia in the Rat", pages 645-650. See entire document.	1-5, 13 1-13
Y	Maladies et Medicaments/Drug and Diseases, Volume 1(1), issued January 1984, (France), Michel et al., "Effects of Aging on Thyroid Status on Brain subcellular Activities. Rat Experimental Study", pages 79-89. See entire document.	1-13

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 03 AUGUST 1994	Date of mailing of the international search report SEP 19 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer PHYLLIS SPIVACK jd Telephone No. (703) 308-1235

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